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10/629,895

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John J. Rossi

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ROTHWELL, FIGG, ERNST & MANBECK, P.C.

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WASHINGTON, DC 20005

EXAMINER

WHITEMAN, BRIAN A

ART UNIT

PAPER NUMBER

1635

NOTIFICATION DATE

DELIVERY MODE

03/30/2010

ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

<b>Office Action Summary</b>	<b>Application No.</b> 10/629,895	<b>Applicant(s)</b> ROSSI ET AL.	
	<b>Examiner</b> Brian Whiteman	<b>Art Unit</b> 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 04 February 2010.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-3,5,6 and 11-16 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-3,5,6,11-16 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948)   | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>2/4/10</u> . | 6) <input type="checkbox"/> Other: _____  |

## DETAILED ACTION

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5, 6, and 11-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

#### **New Matter Rejection:**

The limitation 'corresponding to a secondary stem loop structure of the VA1 transcript' claims 1 and 11 and claims dependent therefrom appears not to be supported by the as-filed specification. Applicant has asserted that there is support for where the limitation in the amended claims is supported, however, there does not appear to be a written description of the limitation in the application as filed. See MPEP § 2163.06. Applicants cite Figure 2C for support of the claimed invention. The Figure only discloses endogenous VA1 RNA containing miRNA. However, the limitation embraces coding sequence selected from heterologous VA1 coding sequences or VA1 coding sequences not identical to the endogenous VA1 transcript. This genus or species embraced by the genus appear not to be disclosed in the specification. Thus,

Art Unit: 1635

the skilled artisan would not be able to reasonably extrapolate from the disclosure in the specification to a genus of VA1 coding sequences corresponding to a secondary stem loop structure of the VA1 transcript.

"It is not sufficient for purposes of the written description requirement of Section 112 that the disclosure, when combined with the knowledge in the art, would lead one to speculate as to modifications that the inventor might have envisioned, but failed to disclose." *Lockwood v. American Airlines Inc.*, 41 USPQ2d 1961, 1966 (CAFC 1997).

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

Art Unit: 1635

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3 and 11-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Agami et al. (US 7,241,618) and Cagnon taken with Doglio et al. (US 5,837,503) in further view of either Yu (AH) or Ambros (Cell, 2001, 107:823-6).

Agami et al. teach making and using an expression cassette comprising an adenoviral VA1 promoter operably linked to an siRNA molecule, wherein the siRNA molecule can be shRNA (columns 50-51 and Figures 8 and 10 and claim 3). Agami et al. teach that siRNA is a substrate for mammalian Dicer (columns 1-3). However, Agami does not specifically teach the structural limitations of the claimed product set forth in claims 1-3.

However, at the time the invention was made, Cagnon teaches inserting an RNAi molecule into a VA 1 expression cassette using a filled-in Not1 site that was ligated into the BstEII cleaved, filled in vector (page 252). In addition, at the time the invention was made, Doglio et al. teach an expression cassette comprising an oligonucleotide has been inserted between or outside the boxes A and B constituting the promoter of said VA gene or into VA1 gene (columns 8, 10-15, and 19-22). Thus, the structural limitations of the product recited in claim 1-3 were known in the prior art for delivering a nucleic acid inhibitor to the cytoplasm of a cell.

Furthermore, at the time the invention was made, Yu teaches an RNA polymerase III vector comprising shRNA can inhibit expression in mammalian cells. Also microRNA was well known to one of ordinary skill in the art as exemplified by Ambros (pages 823-826). Ambros teaches, "Animal genomes contain an abundance of small genes that produce regulatory RNAs of about 22 nucleotides in length (abstract)." "These microRNAs are diverse in sequence and expression patterns, and are evolutionary widespread, suggesting they may participate in a wide range of genetic regulatory pathways (abstract)."

In view of the prior art of record teaching that the stem loop is not cleaved from the VA1 transcript, one of ordinary skill in the art would have been motivated to use the construct taught by Cagnon since the construct results in cytoplasmic transport of the RNAi molecule and Dicer and cytoplasmic RNAi machinery is located in the cytoplasm. Thus, one of ordinary skill in the art would be obvious to try for co-localization of the VA1 transcript with dicer and cytoplasmic RNAi machinery. Also, one of ordinary skill in the art would have had a reasonable expectation for producing the construct or mammalian cell comprising the construct.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Agami and Cagnon taken with Yu in further view of Ambros and Doglio, namely to produce the expression cassette wherein the non-essential stem region contains a BstEII site. One of ordinary skill in the art would have been motivated to combine the teaching to clone the siRNA into the VA1 promoter of the expression cassette since the restriction site is found in an

Art Unit: 1635

adenoviral VA1 promoter and would save time for making another restriction site and producing the construct. "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results."

See **KSR v. Teleflex**, 550 U.S. \_\_\_, 127 S. Ct. 1727 (2007).

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Agami and Cagnon taken with Doglio in further view of either Yu or Ambros, namely to produce a mammalian cell comprising the expression cassette comprising an adenoviral VA1 promoter, wherein an RNAi molecule is contained within a non-essential stem region of the coding region of the VA1 gene. One of ordinary skill in the art would have been motivated to combine the teaching to avoid reducing the activity of the promoter or to determine if RNAi can reduce expression of a target gene in the cell.

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 2/4/10 have been fully considered but they are not persuasive.

Applicant's arguments, see page 7, filed 2/4/10, with respect to the rejection(s) of claim(s) 1, 2, and 11-16 under 103(a) have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of Agami, Cagnon, Doglio, and either Yu or Ambros.

Art Unit: 1635

In response to applicant's argument that the examiner has not cited any prior art nor pointed to any disclosure in the prior art which has been cited that teaches a molecule inserted into a secondary stem loop structure of VA1 transcript is cleaved, the argument is not found persuasive because while Agami, Cagnon, Doglio, and either Yu or Ambros are silent with respect to the limitations 'wherein upon expression the VA1 RNA contains the RNAi molecule which is processed from the VA1 RNA to become a substrate for Dicer' of the instant claims, Agami, Cagnon, Doglio, and either Yu or Ambros makes obvious all of the structural limitations of the claimed product and motivation to produce and a reasonable expectation to make said product, so the functional effect of the claimed product are considered to be inherent of the product.

Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See *In re Ludtke* 441 F.2d 660, 169 USPQ 563 (CCPA 1971). Whether the rejection is based on "inherency" under 35 USC 102, or "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. *In re Best, Bolton, and Shaw*, 195 USPQ 430, 433 (CCPA 1977) citing *In re Brown*, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

In response to applicant's argument that the prior art teaches that there is no motivation to combine the references since the prior art (Cagnon, Doglio, and Rossi (US

Art Unit: 1635

6,100,087)) teaches that inhibitory RNA that had been inserted in a VA1 transcript is not cleaved from the VA1 transcript, the argument is not found persuasive because in view of the prior art of record teaching that the stem loop is not cleaved from the VA1 transcript, one of ordinary skill in the art would have been motivated to use the construct taught by Cagnon since the construct results in cytoplasmic transport of the RNAi molecule and Dicer is located in the cytoplasm. Thus, one of ordinary skill in the art would be obvious to try for co-localization of the VA1 transcript with dicer and cytoplasmic RNAi machinery. .

In response to applicant's argument that the lack of reasonable expectation of success is further supported by post-filing art, where the post-filing art teaches that only the 5' and 3' end of the VA1 transcript that is cleaved by DICER and the remainder of the VA1 transcript is not cleaved by DICER, the argument is not found persuasive because the teaching in the post-filing is not cited in the specification. The teaching in the prior art was unknown at the time the invention was made. Thus, one of ordinary skill in the art would not have been aware of the issue.

Claims 1, 5, and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Agami and Cagnon taken with Doglio and either Yu or Ambros, as applied to claims 1-3 and 11-16 above, and further in view of Lorens (US 2004/0005593).

However, at the time the invention was made, Lorens teaches an RNAi molecule having a loop containing at least 6 nucleotide bases (page 7).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of either Agami, Cagnon, and Doglio taken with either Yu or Ambros and in further view of Lorens, namely to produce an expression cassette comprising an adenoviral VA promoter, wherein an RNAi molecule comprises a loop containing about 8 nucleotide bases. One of ordinary skill in the art would have been motivated to combine the teaching to determine if there is an increase in the inhibition by using a common structure in a shRNA or precursor miRNA molecule to make the expression cassette.

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 2/4/10 have been fully considered but they are not persuasive for the reasons set forth in the previous response to applicant's arguments and applicant has not provided additional argument that need to be addressed.

### ***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

Art Unit: 1635

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number 571-272-0764. The examiner can normally be reached on from 6:30 to 4:00 (Eastern Standard Time). The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor Fereydoun Sajjadi can be reached on 571-272-3311. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Application/Control Number: 10/629,895  
Art Unit: 1635

Page 11

/Brian Whiteman/  
Primary Examiner, Art Unit 1635